LIQUID PREPARATIONS CONTAINING CYCLOSPORIN AND PROCESS FOR PREPARING SAME

FIELD OF THE INVENTION

The present invention pertains to liquid preparations containing cyclosporin, especially cyclosporin A, for oral or parenteral administration, and to a process for preparing same.

BACKGROUND OF THE INVENTION

Cyclosporins are cyclic oligopeptides of microbiological origin, which are used especially as immunosuppressives.

Cyclosporins, especially cyclosporin A, are used in connection with organ transplantation to prevent the rejection of the transplanted organ.

It has also been known that cyclosporins have anti-inflammatory and antiparasitic actions.

Therefore, the use of cyclosporins is not limited to immunosuppressives, but it also includes various autoimmune diseases and inflammatory conditions, especially inflammatory conditions in which autoimmune processes are involved. They include arthritic diseases, e.g., rheumatoid arthritis and rheumatic diseases.

Cyclosporins can be used as antiparasitic agents for the treatment of protozoal infections, e.g., malaria.

However, severe side effects, especially nephrotoxic effects, must be accepted with the cyclosporin formulations currently used in practice.

Cyclosporins are substances of a highly hydrophobic nature. Due to their poor solubility in water, it is difficult to process cyclosporins with the usual pharmaceutical carriers to prepare preparations of sufficient bioavailability.

The cyclosporin-containing pharmaceutical preparations disclosed in the prior art are based on the use of an alcohol and/or oils or similar vehicles in conjunction with a surface-active agent.

U.S. Pat. No. 4,388,307 discloses the solution of cyclosporin in a mixture of transesterification products of various oils formed with polyethylene glycol (e.g., Labrafil M 1499 CS a product of Gattefosse, France), as well as ethanol and a vegetable oil. However, the products thus obtained are unsuitable for intravenous administration because they contain oil. They can be administered only subcutaneously or intramuscularly.

According to product information on the Sandimmun drinking solution sold by Sandoz Pharmeceutical (Chapter XII, Sandoz-Pharma, Basel, 1984), cyclosporin is dissolved in a solution of polyoxyethylated castor oil (e.g., Cremophor EL, available from BASF) and ethanol. The disadvantage of these preparations is the fact that they are poorly tolerated by the patients, because anaphylactic reactions frequently develop (KAHAN et al., *Lancet,* 1984, I:52; LEUNISSEN, K. M. et al., *Lancet,* 1985, I:636).

PCT Application WO 92/09299 discloses oral liquid pharmaceutical preparations which contain a cyclosporin in a mixture of a hydrophilic solvent and a surface-active agent. Polyoxyethylene-polyoxypropylene block polymers (polyoxamers) with molecular weights of 1,000 to 15,500 are used as surface-active agents. The disadvantage of this formulation is the precipitation of the active ingredient in contact with aqueous solutions. These formulations are unsuitable for parenteral administration because of the solubilizing ability of the polyoxamers.

SUMMARY OF THE INVENTION

The goal of the present invention is to provide liquid preparations containing cyclosporin or cyclosporins, which are poorly soluble or insoluble in water, which can be diluted with water in any quantity ratio and form clear, stable solutions.

Another goal of the present invention is to provide formulations which lead to better bioavailability of the active ingredient and thus make it possible to reduce the amount of active ingredient to be administered.

The applicant has surprisingly found that the above-described goals can be accomplished with a solution which contains cyclosporin dissolved in a mixture of a nonionics emulsifying agent such as polyoxyethylene glycerol fatty acid monoester and monohydric and/or polyhydric alcohols, wherein the solutions are stable, well tolerated, have improved bioavailability, and can be administered either orally or parenterally.

More specifically, the present invention pertains to liquid pharmaceutical preparations for oral or parenteral administration, which contain cyclosporin as the active ingredient in combination with a polyoxyethylene glycerol fatty acid monoester and monohydric and/or polyhydric alcohol(s).

DETAILED DESCRIPTION OF THE INVENTION

Polyoxyethylene glycerol fatty acid monoesters (PGFME) are nonionic emulsifying agents, especially those commercially available under the name Tagat from Th. Goldschmidt AG, Germany. Preferred compounds among them are the monoesters of lauric, stearic, oleic and isostearic acids. Especially preferred are the monoesters of oleic acid and lauric acid, which are commercially available under the names Tagat O and Tagat L. The HLB value of the emulsifying agent used is in the range of 10 to 20 and preferably 14 to 17.

The solution concentrations according to the present invention contain 1 to 20 parts by weight of PGFME and 0.5 to 20 parts by weight of the monohydric and/or polyhydric alcohols, preferably 10 to 20 parts PGFME and 2 to 10 parts alcohol and especially 12 to 18 parts of PGFME and 3 to 6 parts of alcohol relative to one part by weight of active ingredient.

All the known natural and synthetic cyclosporins, including their analogs and derivatives, are suitable for use in the preparations according to the present invention. Examples of such cyclosporins are described in, e.g., German Offenlegungsschriften Nos. DE-OS 40,03,844 and DE-OS 40,05,190. Cyclosporin A is preferred.

The active ingredient concentrations in the solutions concentrates according to the present invention are in the range of 20 to 200 mg/mL and preferably 50 to 100 mg/mL.

The alcohol components are monohydric and/or polyhydric alcohols used as individual substances or in random mixtures, e.g., ethanol, propylene glycol and/or polyethylene glycols with a molecular weight of up to 600. Ethanol and/or propylene glycol are preferably used.

In addition, the preparations according to the present invention may optionally also contain other carrier and/or auxiliary substances suitable for intravenous administration, and the preparations intended for oral administration may